



# Role of fibrinogen in trauma-induced coagulopathy

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## Key points

- Fibrinogen levels decrease at an early stage in severe haemorrhage.
- Low fibrinogen levels are associated with increased perioperative bleeding.
- The threshold level for fibrinogen is not defined clearly.
- Early correction using fibrinogen concentrate can improve outcome.

**Summary.** Coagulation defects related to severe trauma, trauma-induced coagulopathy (TIC), have a number of causal factors including: major blood loss with consumption of clotting factors and platelets, and dilutional coagulopathy after administration of crystalloids and colloids to maintain blood pressure. In addition, activation of the fibrinolytic system or hyperfibrinolysis, hypothermia, acidosis, and metabolic changes can also affect the coagulation system. All of these directly affect fibrinogen polymerization and metabolism. Other bleeding-related deficiencies usually develop later in massive bleeding related to severe multiple trauma. In major blood loss, fibrinogen reaches a critical value earlier than other procoagulatory factors, or platelets. The question of the critical threshold value is presently the subject of heated debate. A threshold of 100 mg dl<sup>-1</sup> has been recommended, but recent clinical data have shown that at a fibrinogen level of <150–200 mg dl<sup>-1</sup>, there is already an increased tendency to peri- and postoperative bleeding. A high fibrinogen count exerts a protective effect with regard to the amount of blood loss. In multiple trauma patients, priority must be given to early and effective correction of impaired fibrin polymerization by administering fibrinogen concentrate.

**Keywords:** coagulation; transfusion; trauma

Coagulation defects related to severe trauma have a number of causal factors including: major blood loss with consumption of clotting factors and platelets, and dilutional coagulopathy after administration of crystalloids and colloids to maintain blood pressure. In addition, activation of the fibrinolytic system or hyperfibrinolysis, hypothermia, acidosis, and metabolic changes also affect the coagulation system. All of these directly affect fibrinogen polymerization and metabolism, whereas other bleeding-related deficiencies usually develop later in the course of massive bleeding related to severe multiple traumatized patients. In major blood loss, fibrinogen reaches a critical value earlier than other procoagulatory factors, or platelets. The question of the critical threshold value is presently the subject of heated debate. A threshold of 100 mg dl<sup>-1</sup> has been recommended, but recent clinical data have shown that at a fibrinogen level of <150–200 mg dl<sup>-1</sup>, there is already an increased tendency to peri- and postoperative bleeding. Thus, a high fibrinogen count may exert a protective effect with regard to the amount of blood loss.

Recent findings suggest that fibrinogen availability may play an important role in the survival of trauma patients. The aim of this article is to summarize recent findings regarding changes in fibrinogen availability after traumatic injury. The effects of trauma and blood loss, haemodilution, hyperfibrinolysis, acidosis, and hypothermia are discussed

in the context of fibrinogen availability and the potential benefit of fibrinogen supplementation.

## Trauma-induced coagulopathy

The presence of TIC reflects the extent and severity of injury and correlates with mortality.<sup>1 2</sup> In spite of the rapid use of damage control surgery, the main cause of death in severe trauma, other than head injury, is bleeding, even at specialized centres.<sup>3</sup> In TIC, unlike what occurs in disseminated intravascular coagulopathy, there is no generalized intravascular microcoagulation with subsequent consumption. Instead, there is a bleeding-related loss of coagulation factors and platelets. Subsequently, the remaining procoagulant potential is diluted by the administration of crystalloids and, particularly, by colloids which may also directly affect fibrinogen polymerization.<sup>4</sup> Haemostasis is also fundamentally disturbed by increased fibrinolytic potential, hypothermia, acidosis, anaemia, and electrolyte disturbances, whereas hyperfibrinolysis, hypothermia, and acidosis directly disturb fibrinogen polymerization and metabolism.<sup>5 6</sup> There is a limited increase in fibrinogen synthesis during blood loss which cannot be compensated due to the concomitantly increased fibrinogen breakdown.<sup>2 7</sup> Fibrinogen is present at concentrations of grams per litre which is some 1000-fold higher than other coagulation factors, which are usually in milligrams per litre.

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The aim of any haemostatic therapy is to minimize blood loss and transfusion requirements, and increased transfusion need is known to increase morbidity and mortality in trauma patients. In patients with similar Injury Severity Scores (ISS), mortality is virtually quadrupled as a result of coagulopathy.<sup>1</sup> Massive bleeding or massive transfusion in multiple trauma patients is necessarily associated with impaired coagulation. In simple terms, to achieve adequate haemostasis, sufficient thrombin and coagulable substrate are required. In addition to platelets, on whose surface most of the thrombin is formed, fibrinogen can be regarded as a primary substrate of coagulation.<sup>8</sup> If sufficient thrombin is formed, it converts fibrinogen to stable fibrin, which determines the firmness of the developing clot in the presence of factor XIII.<sup>9</sup>

### Effect of volume replacement therapy on coagulation: dilutional coagulopathy

After trauma and massive bleeding, it is important to achieve normovolaemia to prevent the development of shock and acidosis, which are directly related to coagulopathy and worsen outcome.<sup>10</sup> In this setting, the optimal choice of volume expander remains controversial.

*Crystalloids* compromise the coagulation system chiefly through their diluting effect. Resuscitation with Ringer's lactate reduces tissue hypoxia indices but does not effect the changes in fibrinogen metabolism resulting from haemorrhage.<sup>11</sup>

*Gelatin products* also have a diluting effect and fibrin polymerization is impaired.<sup>12</sup> Decreased clot elasticity, decreased clot weight, and—compared with crystalloid solutions—an increased reduction in the von Willebrand factor have also been reported.

*Hydroxyethyl starch (HES)* solutions may increase haemorrhagic tendency, particularly solutions with a high molecular weight and high degree of substitution. HES causes hypocalcaemia, platelet coating, blockade of the fibrinogen receptor (GPIIb–IIIa), von Willebrand type 1-like syndrome, and a fibrin polymerization disturbance that might exceed the anticoagulant effect of gelatin.<sup>13</sup>

### Hyperfibrinolysis

Hyperfibrinolysis in trauma patients cannot be predicted reliably, but appears to be linked to the severity of the trauma and the organ systems affected (e.g. head injury and urogenital tract injury).<sup>14</sup> Activation of the coagulation system, induced by tissue and endothelial damage, leads to simultaneous release of tissue plasminogen activator (t-PA) and its antagonist, plasminogen activator inhibitor type 1 (PAI-1). Initially, the increase in t-PA appears to outstrip that in PAI-1. In some studies, measurement of the molecular markers of fibrinolysis has shown an increase in fibrinolytic potential, whereas others have found lysis to be decreased as a consequence of trauma. In hyperfibrinolysis, the haemorrhagic tendency can only be treated by giving antifibrinolytics before giving fibrinogen concentrate or, if these are not available, cryoprecipitate. The efficacy of

antifibrinolytics has been well described in cardiac, orthopaedic, and liver (transplant) surgery, but data on their use in severe trauma are lacking.<sup>15</sup>

### Effects of acidosis on fibrinogen metabolism

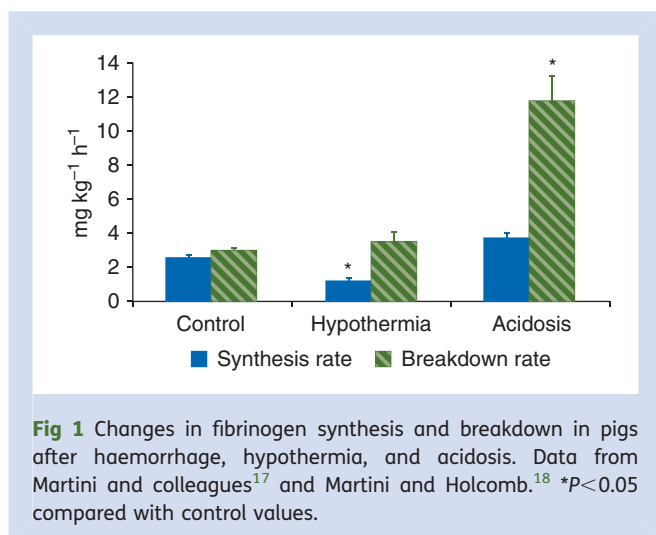
Acidosis can develop as a consequence of trauma and blood loss and is one of the most important predictors of coagulopathy in trauma patients, with the likelihood of death increasing as the severity of acidosis increases. The detrimental effects of acidosis on coagulation include impaired enzyme activity, depleted fibrinogen levels and platelet counts, prolonged clotting time, and increased bleeding time.<sup>16 17</sup>

The mechanisms contributing to the depletions of fibrinogen were studied recently in a swine model where acidosis of pH 7.1 was induced by an infusion of 0.2 N HCl in lactated Ringer's solution (LR).<sup>18</sup> When the target pH of 7.1 was achieved and Lactated Ringer's solution stabilized, stable 1-<sup>13</sup>C-phenylalanine was infused for 6 h and d<sub>5</sub>-phenylalanine was infused for 4 h. Blood samples were obtained hourly during the infusion and the isotopic labelling of fibrinogen was determined using gas chromatography and mass spectrometry analysis. This study showed that acidosis increased fibrinogen breakdown by 1.8-fold compared with control values, with no effects on fibrinogen synthesis.<sup>18</sup> Thus, it appears that acidosis had different effects on fibrinogen synthesis and breakdown and there was a potential depletion of fibrinogen availability after acidosis.

### Effects of hypothermia on fibrinogen metabolism

Hypothermia, with a body temperature of  $\leq 34^{\circ}\text{C}$ , is commonly observed in severely injured patients. The relationship of hypothermia to abnormal coagulation and mortality has been well described. In a group of trauma patients with ISS  $>25$ , the mortality increased from 10 to 100% when body temperature declined from 35 to  $<32^{\circ}\text{C}$ .<sup>19</sup> Around 80% of those who did not survive had a body temperature of  $<34^{\circ}\text{C}$  at the time of death.<sup>20</sup> The known adverse effects of hypothermia on coagulation include prolonged prothrombin time and activated partial thromboplastin time in hypothermic patients and animal experiments, and in plasma samples cooled *in vitro*.<sup>21 22</sup>

The effects of hypothermia on fibrinogen metabolism and coagulation function were investigated in a normovolaemic swine model.<sup>23</sup> Hypothermia of  $32^{\circ}\text{C}$  was induced using a cold blanket with circulating water at  $4^{\circ}\text{C}$ . When the temperature was stabilized at  $32^{\circ}\text{C}$ , 1-<sup>13</sup>C-phenylalanine and d<sub>5</sub>-phenylalanine were infused to quantify fibrinogen metabolism.<sup>23</sup> Hypothermia of  $32^{\circ}\text{C}$  decreased fibrinogen synthesis, with no effects on fibrinogen degradation (Fig. 1). Fibrinogen synthesis and degradation are regulated via different mechanisms and there is also a potential deficit in fibrinogen availability after hypothermia.



**Fig 1** Changes in fibrinogen synthesis and breakdown in pigs after haemorrhage, hypothermia, and acidosis. Data from Martini and colleagues<sup>17</sup> and Martini and Holcomb.<sup>18</sup> \* $P < 0.05$  compared with control values.

## Interaction of platelets with fibrinogen

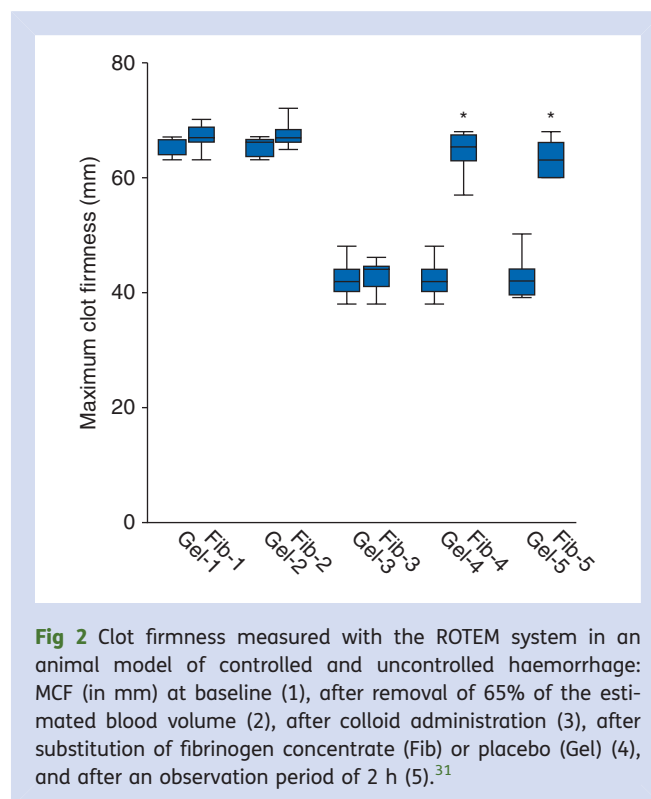
International recommendations suggest replacement using platelet concentrates should be given for trauma- or surgery-related bleeding if the platelet count decreases below  $50\,000\ \mu\text{L}^{-1}$ .<sup>24</sup> A lack of platelets primarily affects clot firmness, which is also influenced by fibrinogen plasma level. To assess an individual's need for replacement therapy, thrombelastographic (TEG®)/thrombelastometric (ROTEM®) measurements of clot firmness in relation to fibrinogen polymerization can provide valuable information, as strong fibrin polymerization can compensate for the decreased platelet contribution to clot firmness. Thrombocytopenic patients with inflammation-induced elevated fibrinogen values in TEG®/ROTEM® monitoring are often not transfused with platelet concentrates because the clot firmness is within the normal range.

An animal study found that the administration of fibrinogen concentrate significantly improved clot firmness in comparison with the transfusion of 3-day-old aphaeresis concentrates or placebo.<sup>25</sup> In uncontrolled bleeding, the fibrinogen-treated animals had significantly lower blood loss and longer survival times than animals given platelet concentrate and placebo.

## Fibrinogen replacement in TIC

It may be thought that coagulation disturbances should not be treated until the source of the bleeding has been surgically dealt with. A strong counterargument to this is that this delay reduces the haemostatic potential to such a degree that surgery becomes much more difficult and microvascular bleeding in non-injured organ systems can occur. The resulting deficit can be so pronounced that conventional coagulation therapies will fail.

As a consequence of blood lost, dilutional coagulopathy, hypothermia, and acidosis, fibrinogen may reach critical levels at an early stage in multiple trauma patients with massive bleeding. Even small quantities of colloids ( $>1000$



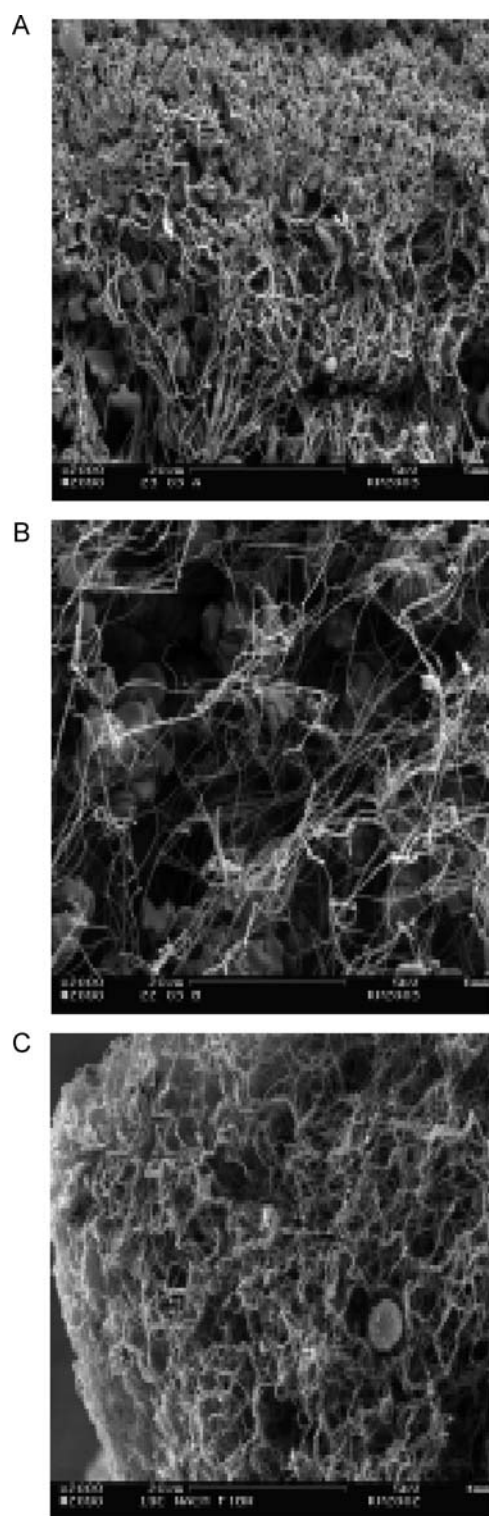
**Fig 2** Clot firmness measured with the ROTEM system in an animal model of controlled and uncontrolled haemorrhage: MCF (in mm) at baseline (1), after removal of 65% of the estimated blood volume (2), after colloid administration (3), after substitution of fibrinogen concentrate (Fib) or placebo (Gel) (4), and after an observation period of 2 h (5).<sup>31</sup>

ml) can impair fibrin polymerization.<sup>13</sup> Normovolaemic dilution can cause the critical fibrinogen concentration to be reached even before administration of red blood cells becomes necessary.<sup>26</sup> As discussed above, the critical fibrinogen value is unclear with some recommending  $100\ \text{mg dl}^{-1}$ <sup>27</sup> or even  $50\ \text{mg dl}^{-1}$ <sup>28</sup> adequate. These recommendations also do not take account of the fact that plasma fibrinogen measurements, both in the high and the very low range, are not readily standardized. They can be distorted upwards by the use of colloids and, particularly, HES<sup>29,30</sup> and do not agree with functional measurements.<sup>13</sup>

The influence of fibrinogen concentrate has been examined in several animal models of uncontrolled bleeding. In one model, 65% of the estimated total blood volume was withdrawn from pigs and compensated with gelatin to induce severe dilutional coagulopathy. Fibrinogen concentration or a placebo was subsequently administered. The compensation with fibrinogen concentrate normalized the impaired clot strength (Figs 2 and 3). The animals who received fibrinogen concentrate showed statistically significantly less blood loss after a stab incision to the liver.<sup>31</sup>

Clinical data from gynaecological, neurosurgery, and cardiac surgery show that perioperative and postoperative haemorrhagic tendency is increased when fibrinogen levels are below  $150\text{--}200\ \text{mg dl}^{-1}$ .<sup>32–37</sup> Data on the efficacy of fibrinogen concentrates in acquired fibrinogen deficiency are limited. Observational reports from clinical use and retrospective data analyses have shown that fibrinogen concentrate is able to stabilize reduced clot strength.<sup>38–40</sup> During spinal or large craniofacial operations, reduced clot strength





**Fig 3** Electron microscopic scan of a  $\times 2000$  magnified blood clot in a non-diluted state (A), after 65% haemodilution with gelatin (B), and after administration of fibrinogen concentrate to compensate dilutional coagulopathy (C). The administration of fibrinogen was able to compact the rarefied fibrin network again.<sup>31</sup>

was improved by administering fibrinogen concentrate alone.<sup>41</sup> A retrospective study in 252 seriously injured soldiers who received massive transfusion correlated the amount of fibrinogen given (a combination of cryoprecipitate and fresh-frozen plasma) and survival.<sup>42</sup>

Four other small prospective clinical studies have examined the use of fibrinogen concentrate (ROTEM<sup>®</sup>-assisted in two studies). In all four studies, coagulation was optimized, perioperative bleeding was reduced by 32%,<sup>43</sup> and transfusion requirement was significantly reduced.<sup>44–46</sup>

In summary, a high circulating fibrinogen exerts a protective effect with regard to blood loss. In clinical practice, TEG<sup>®</sup> or ROTEM<sup>®</sup> monitoring simplifies and improves coagulation monitoring and management. In bleeding which requires transfusion, fibrinogen concentrate (or cryoprecipitate) should be administered if the maximum clot firmness (MCF) in the FIBTEM<sup>®</sup> analysis is below 10–12 mm, the 10 min value is below 7 mm (depending on the clinical situation), or both. If ROTEM<sup>®</sup> monitoring is not available, fibrinogen plasma levels should be maintained at a minimum of 150–200 mg dl<sup>-1</sup>.

In conclusion, fibrinogen availability is regulated through dynamic changes of synthesis and breakdown to maintain coagulation function. Recent studies have shown the role of fibrinogen availability in TIC. Haemodilution, hyperfibrinolysis, acidosis, and hypothermia all depleted fibrinogen availability and consequently impair coagulation process. Recent retrospective studies in trauma patients and animal models suggest that fibrinogen supplementation may be beneficial. Further prospective clinical trials to confirm the benefits of fibrinogen supplementation in trauma patients with TIC are warranted.

## Conflict of interest

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